REMARKS

Status

Claims 66-68 and 73-84 are present in the application, with Claims 66-68 and 73-75 under active consideration. Claims 1-65 and 69-72 are canceled. Claims 76-80 have been withdrawn by the Examiner. Claims 81-84 have been added by this Amendment. Upon entry of the claim amendments above, Claims 66, 76 and 81 are independent. Support for new Claims 81-84 is found in the specification at page 26, lines 24-25; page 62, lines 6-10; page 65, lines 1-30 and throughout the specification. The other amendments are editorial in nature or to more particularly define the invention.

Accordingly, this amendment incorporates no new matter.

Improper Non-Examination of Claims

Applicants note that Claims 76-80 are drawn to the same statutory class of invention as the claims under examination. No proper basis for a Restriction Requirement under 35 U.S.C. § 121 has been established. In addition, Claims 76-80 contain many overlapping elements including the specific sequence data associated with Human MIF thereby negating any reasonable basis for a burdensome search. Claims 76-80 were properly presented before final. Accordingly, Applicants respectfully request that claims 76-80 be rejoined and examined on the merits.

Personal Interview

Applicant's gratefully acknowledge the Examiner's kind consideration during the Personal Interview on January 28, 2003.

Claim Rejections under 35 U.S.C. § 102

Claims 66-68 and 73-74 are rejected under 35 U.S.C. § 102(e) as purportedly anticipated by Ishizaka et al., U.S. Patent No. 5,786,168. Applicants respectfully traverse.

Applicants respectfully point out that the claims are directed to a diagnostic method for

determining the amount of MIF protein in a sample, comprising (a) obtaining a sample; and (b) determining the amount of MIF in the sample using an immunoassay with an anti-MIF antibody, wherein the immunoassay is selected from the group consisting of ELISA, immunoprecipitation, immunohistocytochemistry, and Western analysis, and wherein MIF is a human MIF polypeptide having a molecular weight approximately 12.5 kDa, and wherein the anti-MIF antibody binds to the 12.5 kDa human MIF consisting of the amino acid sequence of SEQ ID NO: 5.

The Ishizaka et al. patent fails to teach the claimed invention, expressly or inherently. Ishizaka et al. is directed to Glycosylation Inhibitory Factor (GIF) and its involvement in physiology and pathology. GIF is not Macrophage Migration Inhibitory Factor (MIF). As Ishizaka et al. states at column 2, lines 60-64, it is uniquely identified by its biological properties and it undergoes at least one post-translational modification in phosphorylation that is not associated with MIF.

> "A unique property of GIF is its biochemical activity. This lymphokine binds to monoclonal antibodies against lipomodulin (a phospholipase inhibitory protein) and appears to be a phosphorylated derivative of a phospholipase inhibitory protein (Uede, et al., J. Immunol, 130: 878, 1983)."

GIF does not exhibit MIF biological properties as Ishizaka et al. points out at column 46: "The results indicated that rhGIF was different from MIF in biological activity." Ishizaka et al. is acknowledging in the document itself that there is a structural distinction between GIF and MIF

The Office Action propounds a legal and factual approach which is not supportable on any ground. The Examiner states the basis for maintaining his rejection as follows: "All that is necessary is an antibody which specifically binds SEQ ID NO.5. Since the prior art teaches an antibody which specifically binds to SEQ ID NO:5, the claim is anticipated." See the Office Action mailed October 6, 2003, page 3, last paragraph.

By this approach the Examiner overlooks the legal requirement that a reference must disclose the all elements of a claim in order to anticipate. Even if this basic tenet of patent law were excused, there is no adequate basis for the assertion that an antibody that binds to GIF will also bind to SEQ ID NO:5 in MIF.

The Examiner has failed to establish that any element in the claim is disclosed in Ishizaka et al., but adheres to the mistaken understanding that the disclosure of an antibody that may bind GIF will also bind MIF, and that this ostensibly anticipates the claim. Nevertheless, the claim involves other elements than simply an antibody that binds MIF. For instance, the reference does not disclose MIF as the diagnostic target. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Furthermore, *assuming arguendo*, that the disclosure of merely an antibody that fell within the scope of the claim were sufficient to anticipate the claim, the Examiner is mistaken in that there is no adequate basis to assert that an antibody that binds to GIF as in Ishizaka et al. will necessarily bind to MIF. Despite the assertion in the Office Action to the contrary, the fact that two different proteins (MIF and GIF) may share a similar partial sequence does not mean that an antibody to one protein will necessarily bind to the other protein.

As was discussed in the interview referenced above, there is homology between SEQ ID NO: 38 in Ishizaka et al. and SEQ ID NO:5 as designated in Applicants Claim. However, an antibody does not necessarily bind to a sequence coded by DNA, but instead binds to the final form of the active protein. The sequence SEQ ID NO: 38 is a "deduced" sequence taken from the

DNA code for GIF. SEQ ID NO: 38 does not necessarily represent an actual protein sequence for GIF as the sequence coded by the DNA can undergo numerous forms of further change that will affect the conformation, the chemical structure, the glycosylation patterns and the biological activity of the final molecule.

It is common knowledge that antibodies bind to proteins based not only on the primary protein structure (i.e., the linear sequence), but also based on the combination of primary, secondary, tertiary, and perhaps also, the quaternary protein structure that all contribute to the three-dimensional folding of the target protein. In addition, GIF has other structural distinctions without parallel in MIF such as cysteinylation, phosphorylation and complexation. Hence, there is no way to account for how these changes will impact the final three-dimensional structure of the GIF protein.

There are still more reasons to doubt that an antibody that binds a GIF will also bind MIF. Ishizaka et al. notes that there is more than one form of GIF, at column 2, line 67 et seq.

> "Subsequent experiments on ovalbumin (OVA)-specific suppressor T-cell hybridomas indicated that stimulation of the hybridoma cells with antigen (OVA)-pulsed syngeneic macrophages resulted in the formation of GIF that has affinity for OVA (antigen-binding GIF). However, the same hybridomas constitutively secreted GIF having no affinity for OVA (nonspecific GIF). Studies on the relationship between nonspecific GIF and OVA-binding GIF indicated that the antigen-binding GIF is composed of an antigen-binding polypeptide chain and a nonspecific GIF"

Ishizaka et al. as stated in the patent at column 5, lines 14-18 is directed to one type of GIF:

"The present invention relates to substantially pure human antigen-specific GIF with specificity for an antigen associated with an undesirable immune response. This human antigen-specific GIF is highly useful for the immunosuppression of the undesirable immune response in an antigen-specific manner."

So it is still more suspect that an antibody that binds to a GIF will necessarily bind to MIF.

For instance, the antibodies produced in Example 5 of Ishizaka et al. will be specific in their binding to GIF produced in the T-Cell hybridoma CL3. See column 26, lines 1-10. In fact, Ishizaka et al. is directed to producing antibodies that are not only specific in their binding to human GIF, but are even more specific in the antibody binding to the form of GIF describes as "antigen-binding GIF." See column 9, lines 9-31, and in particular lines 29-31:

"The monoclonal antibodies of the invention can also be used in immunoaffinity chromatography for the purification of the various types of human GIF mentioned herein."

There is extremely little likelihood that antibodies designed to differentiate between forms of GIF would also bind MIF. Even if all or part of the homologous linear sequence might be present on the GIF protein exterior, the folding involved in that protein in all likelihood presents completely foreign binding sites to those that are presented from the three-dimensional structure of MIF. Although it is within the realm of theoretical possibility that an antibody to one might bind to another, this does not meet the anticipation by inherency requirement that such a disclosure must necessarily be present. The possibility that a disclosure may be inherent is not sufficient. See MPEP 2112.

The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based

on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted).

Therefore, Ishizaka et al. fails to anticipate the claims. Accordingly, reconsideration and withdrawal of the anticipatory rejection is respectfully requested.

CONCLUSION

All rejections having been addressed by the present response, Applicants assert that the present case is in condition for allowance and respectfully request early notice to that effect. If any issues remain to be addressed in this matter which might be resolved by discussion, the Examiner is respectfully requested to call Applicants' undersigned counsel at the number indicated below.

Respectfully submitted,

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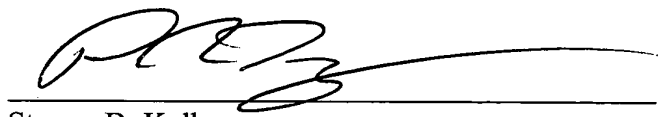

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ABSTRACT

A diagnostic method for determining MIF content in a sample using a direct or an indirect detection technique and wherein MIF is a human MIF polypeptide having a molecular weight of approximately 12.5 kDa.